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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/598,885	09/14/2006	Jakob Busch-Petersen	PU60791	1731

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EXAMINER	
SZNAIDMAN, MARCOS L	

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
02/22/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/598,885	BUSCH-PETERSEN ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,8-10 and 13-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6, 8-10 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6 pages*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of the following species: {4-[2-(1,4-dihydro-1,4-epiazano-naphtalen-9-yl)-ethyl]-cyclohexyl}-amide, in the reply filed on December 14, 2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of Claims

Cancellation of claims 5, 7, 11 and 12; addition of claims 13-20, and amendment of claims 1-3, 6, 8 and 10 in the reply filed on December 14, 2007 is acknowledged.

Claims 1-4, 6, 8-10, and 13-20 are currently pending and are the subject of this office action.

Claims 1-4, 6, 8-10, and 13-20 are presently under examination.

Priority

The present application is a 371 of PCT/US04/08025 filed on 03/17/2004.

Claim Rejections - 35 USC § 112

Claims 1-4, 6, 8-10, and 13-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to a composition and a method of treating a muscarinic acetylcholine receptor mediated disease, selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis in a mammal in need thereof comprising administering to said mammal an effective amount of a compound according to claim 1 ({4-[2-(1,4-dihydro-1,4-epiazano-naphtalen-9-yl)-ethyl]-cyclohexyl}-amide is the elected species).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

The factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and physiological activity is considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors,

such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved); *Nationwide Chemical Corporation, et. al. v. Wright, et. al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances); *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable); *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian vaccine was uncertain).

Regarding more specifically to the treatment of respiratory diseases with muscarinic acetylcholine receptor antagonists, the examiner cites: Goodman & Gilman's (The Pharmacological basis of Therapeutics, 10th edition, 2001, pages 162-171). Although there is evidence that muscarinic acetylcholine receptor antagonists might be useful for the treatment of some respiratory diseases, so far, there are only three compounds of this class approved for the treatment of respiratory diseases: Ipartropium bromide (Atrovent), Oxitropium Bromide and Tiotropium Bromide (Spiriva) (See structures on page 163, Figure 7-2, the structure of Oxitropium Bromide is not shown, but is a N-ethyl-substituted, quaternary derivative of scopolamine, see also page 168 under Synthetic and semisynthetic substitutes for belladonna alkaloids). These compounds show a very tight structure-activity relationship (see page 164 under Structure-Activity Relationship): an intact ester of tropine and tropic acid is essential for

antimuscarinic action, since neither the free acid nor the base exhibits significant antimuscarinic activity. The presence of a free OH group in the acyl portion of the ester is also important for activity. When given parenterally, quaternary ammonium derivatives of atropine and scopolamine are, in general, more potent than their parent compounds in both muscarinic receptor and ganglionic blocking activities. So, it will be very hard to predict if a compound without the structural characteristics described above, could possibly be a muscarinic acetylcholine receptor antagonist, even less an effective treatment for a respiratory disease.

2. The breadth of the claims

Even though the current examination is restricted to the elected species: ({4-[2-(1,4-dihydro-1,4-epiazano-naphtalen-9-yl)-ethyl]-cyclohexyl}-amide), applicant should be aware that the claims vary in breadth: for example, claim 1 recites a broad genus of compounds, probably in the millions and claim 6 recites a broad genus of respiratory diseases.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification only provides the recipes for an *in vitro* (inhibition of receptor activation by calcium mobilization) and *in vivo* (methacholine-induced bronchoconstriction in mice) assay, but no experimental data for any of the compounds claimed, including the elected species, is offered.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept that instantly claimed compound ({4-[2-(1,4-dihydro-1,4-epiazano-naphtalen-9-yl)-ethyl]-cyclohexyl}-amide, or any of the compounds of claim 1, could be predictably used as treatment for any of the respiratory diseases listed in claim 6. Since there is no precedent in the literature that any of these compounds could possibly be a muscarinic acetylcholine receptor antagonist, since they lack the structural features that the literature suggests is required for such activity (see above discussion), and since applicant did not provide experimental data that supports that claim; determining if the elected species (or any of the non-elected compounds), would be a useful treatment of any respiratory disease, would require testing these compounds in an in vitro assay to determine, which, if any, of these compounds has antimuscarinic activity, then an in vivo functional assay in some animal model to determine if they are efficacious against any respiratory disease, formulation into a dosage form, and subjecting into clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claims 1-4, 6, 8-10, and 13-20 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to

practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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